Thesis title: Decision-making under Ambiguity in Neurodegenerative Disease

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1. Introduction

1.1 Decision-making as an aspect of Executive Dysfunction

Decision-making is a complex skill that is essential for daily life. Yet the complexities of this process are often overlooked in favour of more obvious cognitive deficits during neuropsychological assessment, such as memory or attention impairments. Decision-making involves affective and motivational aspects of executive functions (Happaney, Zelazo & Stuss, 2004). Executive functions include a range of abilities that can be divided into three categories: 1) goal setting and planning, 2) action initiation and sequencing and 3) self-monitoring and inhibition (Gurd, Kischka & Marshall, 2010). Executive functions enable us to deal with unforeseen events and orchestrate our responses in order to lead independent functional lives. They refer to our higher cognitive processes of awareness and self-regulation. Executive dysfunction can result in problems such as impulsivity, perseveration and disinhibition (Gurd, Kischka & Marshall, 2010). These negative behaviours can clearly impair effective decision-making, as patients with executive dysfunction may not weigh up the pros and cons of a situation appropriately. Successful decision-making involves careful consideration of the available stimuli and their value, in order to access the situation adequately. These stimuli may be emotional, for example, we interpret facial expressions continuously to avoid disappointing or upsetting others. Stimuli may also be motivational in terms of whether they are required for future purposes, for example, we will not throw away something we have previously learned could be useful in the future. Stimulus evaluation and consequence anticipation are essential for successful decision-making, and executive impairments such as impulsivity, perseveration and disinhibition can affect these processes.

The everyday implications of a decision-making impairment can be diverse and devastating. Patients in the early stages of neurodegenerative diseases remain active agents in making decisions regarding their treatment plan, medications, living arrangements and finances, to name but a few (Sinz et al., 2008). Therefore the importance and urgency in accessing any decline in decision-making abilities is clear to prevent potentially serious repercussions. Hence research into how we make decisions in different circumstances, what brain regions are involved and how they are affected by neurodegenerative diseases, is worthwhile and ecologically valid.

1.2 Conditions of decision-making

Three conditions have been investigated in studies concerning decision-making: risk, ambiguity and certainty. Risky decisions are those made with explicit rules regarding possible rewards or punishments, whereas decisions under ambiguity are those made using implicit rules (Sinz et al., 2008) and decisions made under certainty are not followed by rewards or punishments (Fellows & Farah, 2007). For example, decisions under certainty have been investigated by Fellows and Farah (2007) using a preference judgement task. Participants were asked to choose between a series of two items and state which they preferred. This task involves evaluation and comparison of items if choices are to be made based on preference, not arbitrarily. These decisions were not followed by gains or losses. However risky decisions are made using explicit rules to observe and judge the probability of gains and losses involved on each trial e.g. Cambridge Gambling Task (Rogers et al., 1999). Lastly, decisions under ambiguity are followed by gains or losses based on implicit rules that the participant must discover through trial and error e.g. Iowa Gambling Task (IGT; Bechara et al., 1994). The IGT is a classic decision-making task in which participants are presented with four card decks and the aim to try and win as much money as possible. Card selections are followed by wins and/or losses and participants must discover which decks are more advantageous over time, using implicit rules only. Ambiguous decision-making is perhaps the most complex as the rules are not overt and we require these skills everyday to interpret the world around us. Henceforth, decision-making under ambiguity will remain the focus of this study.

1.3 Brain regions involved in decision-making

Decision-making, as an aspect of executive functioning, is associated with the prefrontal cortex (Rogers et al., 1999b). The prefrontal cortex can be subdivided into three main areas: medial/cingulate cortex (MC), orbitofrontal cortex (OFC) and the lateral prefrontal cortex (LPF) (Gurd, Kischka & Marshall, 2010). Oftentimes, studies involving the OFC region refer more generally to the ventromedial frontal cortex (VMF) which includes the OFC and the ventral portion of the medial wall of the frontal lobe (Fellows & Farah, 2003, 2007). Henceforth, OFC and VMF will be used somewhat interchangeably. The OFC is involved in representing the reward and punishment value of stimuli as well reversing learned associations between stimuli and rewards and punishments (Rolls, 2000).

In the classic case of Phineas Gage (Harlow, 1848), a responsible, pleasant man was struck by an iron rod that penetrated his VMF in a mining accident. The behavioural changes observed were so drastic that friends said he was no longer himself. He became impatient and stubborn, unpredictable and indecisive, unable to settle on any of the plans he devised for the future. Increased impulsivity affects decision-making in that salient stimuli are not evaluated appropriately and the consequences of one's actions are not considered in advance. E.V.R. (Bechara et al., 1994) is a patient with ventromedial damage to the prefrontal cortex, who performed normally on laboratory tests such as the Wisconsin card sorting task (Milner 1963) and cognitive estimates (Shallice & Evans, 1978), yet whose decisions frequently resulted in negative outcomes. Evidently, decision-making can be impaired despite other cognitive functions remaining intact. Rolls and colleagues (1994) describe the insensitivity of patients with VMF damage towards others and how impaired decision-making can affect personal relationships. Therefore it is apparent that OFC damage can result in devastating behavioural changes.

Decision-making requires the integration of cognitive and emotional input as well as emotion processing. The amygdala has strong connections with the OFC in relation to emotion processing and decision-making (Happaney, Zelazo & Stuss, 2004), as does the striatum (Hsu et al., 2005) and the basal forebrain (Sinz et al., 2008). The OFC and amygdala are often activated simultaneously in tasks that require evaluation of stimuli or the detection of stimuli with a salient value. Together they activate reward related signals to motivate behaviour (Hsu et al., 2005).The value of salient stimuli in terms of reward and punishment is often the basis of decision-making. When information necessary for decision-making is absent from the environment, the brain is alerted to its absence as the situation may prove dangerous. A range of cognitive and behavioural resources are activated to extract as much information from the environment as possible to avoid punishment (Hsu et al., 2005). When stimuli cease to be rewarding/punishing, behaviour is modified.

Rolls and colleagues (2008) suggest, with evidence from single neuron neurophysiology in non-human primates, that the OFC contains many subsets of neurons that each hold particular value representations for particular rewards. The medial OFC has been suggested to be involved in the learning of reward values and maintenance of advantageous strategies, whereas the lateral OFC is thought to be involved in altering these strategies when rewards become inconsistent i.e. reversal learning. This functional dissociation has been investigated using functional neuro-imaging

techniques (O' Doherty et al., 2001, Lawrence et al., 2008). Reversal learning is intrinsic to effective decision-making as advantageous decision- making relies on stimulus evaluation and re-evaluation. The value of certain stimuli may not be realised if the individual is unable to reverse their initial learning between stimuli, rewards and punishments, as its value depends on situational dynamics.

Reward processing and reversal learning both have clear roles in decision-making. Reversal learning involves rapid behavioural modification by stimulus-reinforcement association relearning, when reward/punishment stimuli associations vary or reverse (Rolls, 2000). Patient's with OFC damage fail reversal learning tasks as they repeatedly respond to stimuli that have ceased to be rewarding (Rolls et al., 1994). The amygdala is involved in the initial processing of reward stimuli. However reappraisal of the stimuli once it has ceased to be associated with rewards is in the domain of the OFC (Happaney, Zelazo & Stuss, 2004). Fellows and Farah (2003) specifically found the VMF (outlined as overlapping with the posteromedial OFC according to their lesion analysis) to be key in reversal learning, in a study involving patients with frontal lesions. Reversal learning, according to their paradigm, involves affective shifting as stimuli are associated either with rewards or punishments. They state that VMF damage does not result in a general learning deficit as initial learning was not affected in a group of patients with frontal lesions. The degree of additional damage to neighbouring ventral and medial frontal structures did not mediate the degree of their reversal learning impairment

The social ramifications resulting from deficits in stimulus reappraisal are vast as re-evaluation of social cues is vital for appropriate decision-making. In dynamic social contexts, we re-evaluate facial expressions, gestures and many other social cues to adapt our behaviour to a manner that is considered socially appropriate. . Fellows and Farah (2003) also found a negative association between reversal learning and the instrumental activities of daily living scale. Rolls and colleagues (1994) also found reversal learning to be correlated with behavioural change in a group of frontal patients. Therefore the importance formulating a task to investigate reversal learning deficits is ecologically valid as impairments in this domain can really affect the day-to-day lives of patients and carers.

Hornak and colleagues (1994) devised a reversal learning task in which two simple patterns appear together on screen. Participants are told that both patterns involve monetary gains and losses.

However, they are warned that one pattern was higher rewards than losses, whereas the other pattern has higher losses than rewards. Therefore there is a “good” pattern and a “bad” pattern. Participants are told to find the “good” pattern through trial and error, and once they think they have found it, they must select it continuously. Participants are told that the patterns switch an indefinite amount of times throughout the task, i.e. that the “good” pattern becomes the” bad”, and the “bad” pattern becomes the “good”. They are urged to pick up on these reversals as quick as they can through trial and error. The aim of the game is to keep track of which pattern is currently the “good” one. Therefore participants must learn which pattern is good through the evaluation of rewards and punishments. They are then required to reverse what they have previously learned about each pattern once the switch occurs. As reversal learning is thought to involve the OFC (Rolls et al., 2000), this task and other like it have great potential to investigate reversal learning deficits in patients with neurodegenerative diseases which may reflect OFC involvement if performance is impaired.

The Iowa gambling task (IGT; Bechara et al., 1994) is another decision-making task with a reversal learning element, thought to activate the OFC and the dorsolateral prefrontal cortex (DLF). The IGT consists of four card decks. Participants are asked to select cards from any of the four decks and can switch between decks as often as they like, for 100 card selections. After each card selection, participants win or lose an amount of money. “Good” decks have lower wins but lower losses, and “bad” decks have higher wins but also higher losses. Participants are urged to treat the money in the task, as if it was real money and hence to make decisions as if they were dealing with their own money. Participants are told that once they have figured out which decks are the “bad” ones, to avoid them. The aim of the game is to win as much money as possible. It is not explicit which decks are “good” and which are “bad”, decisions must be made through trial and error initially and gradually implicit patterns should be picked up on. Therefore the IGT is a decision-making task under ambiguity, as which decks are advantageous and which decks are disadvantageous is not explicitly known. Participants usually develop a preference for the “bad” decks initially, as they contain higher wins. No losses occur until after the first 8 card selections of each deck. Once losses appear, participants must reverse their initial strategy and begin to make selections from the lower wins/losses decks which are more advantageous in the long run. Therefore the original IGT involves reversal learning,

Patients with VMF lesions are impaired on the IGT compared to controls (Bechara et al., 1994, Fellows & Farah, 2004). Patients with VMF lesions are impaired on the IGT due its reversal learning aspect (Fellows & Farah, 2005). Participants select the high wins/losses initially and then they must reverse their strategy once punishments appear after the first 8 card selections. They then realise that the low wins/losses decks are more advantageous overall. To investigate this further, Fellows and Farah (2005) administered a shuffled version of the IGT. The shuffled version was exactly the same as the original, except the first 8 cards are taken from the top of the decks and moved to the bottom. Therefore, the first 8 cards of each deck are no longer only wins, and losses are experienced earlier and more frequently. Hence the shuffled IGT does not involve reversal learning as participants do not need to "un-learn" which decks are more advantageous. VMF patients' performance improved to that of controls when the reversal element of the task was controlled for. This is most interesting at it means that original IGT performance is impaired in VMF patients due to its reversal learning aspect not due to reward hypersensitivity, punishments insensitivity or future consequence insensitivity as Bechara and colleagues (1994) predicted.

However the shuffled variant of the IGT was impaired in a separate group of DLF patients in Fellows and Farah's study (2005). DLF damage resulted in impaired IGT performance on both the original and the shuffled variant (Fellows & Farah, 2005). Hence Fellows and Farah (2005) suggest DLF damage relates to working memory impairment as the IGT does have a strong working memory element. Bechara and colleagues (1994) also speculated that working memory deficits may account for what they called "myopia for the future". They suggest that patients may not be able to hold representations of future outcomes in their working memory long enough for attentional control processes to convert these representations into strategies. Therefore within the decision-making tasks discussed, two main areas of the frontal lobe have been implicated: OFC/VMF and the DLF. Their varying level of involvement depends on whether the task involves basic stimulus reinforcement evaluations and advantageous strategy formation, or perhaps the more complex reversal of stimulus-reinforcement associations. Henceforth a selection of neurodegenerative diseases will be discussed that are known to involve the aforementioned brain regions and hence their decision-making abilities will be investigated.

1.5 Frontotemporal Dementia and Decision-making

Frontotemporal dementia (FTD) is a degenerative brain disorder and consists of three distinct subtypes: behavioural/frontal variant FTD, semantic dementia/temporal variant FTD and Progressive Non-fluent Aphasia. For the purposes of this study, we will be investigating only the behavioural variant of FTD and will refer to it simply as FTD from here onwards as a subtype of the broader term frontotemporal lobar degeneration, (Neary et al., 1998). In FTD patients, brain-imaging techniques identify focal asymmetric frontal atrophy oftentimes coupled with temporal atrophy (Doherty et al., 2011). They suggest that atrophy begins in the orbitofrontal and cingulate cortices and progress towards the basal ganglia and insular cortex.

The Lund and Manchester groups (1994) characterise FTD as follows: insidious onset before 65 and slow progression with early loss of personal awareness, social awareness and insight into the fact that changes in current state are a product of neuropathology. Other behavioural symptoms include disinhibition and utilisation behaviours, impulsivity, mental rigidity or inflexibility, hyperorality, as well as stereotyped and preservative behaviours. Cognitive impairment in FTD primarily involves executive dysfunction. FTD patients have been found to be impaired on the Tower of London (Rahmann et al., 1999). However more traditional executive functioning tests, e.g. Wisconsin card sorting task and verbal fluency, are not sensitive enough to detect the type of executive dysfunction FTD patients experience (Gregory et al., 2002).

More ecologically valid tests of executive functioning, e.g. the Multiple Errands Task, can highlight impairment in FTD patients with otherwise preserved cognitive functioning, as measured by the ACE-R (Torralva et al., 2009). In this study the IGT is also used as an ecologically valid executive functioning task as it involves planning and complex decision-making skills. Again FTD patients with high ACE-R scores (above cut-off score of 88), who failed to showed impairment on traditional tests, were impaired on the IGT. Therefore the IGT is sensitive for investigating executive impairment in for both low and high cognitive functioning FTD patients.

Even FTD patients early on in their illness were found to be impaired on the IGT (Torralva et al., 2007). FTD patients made more disadvantageous than advantageous deck selections, whereas all controls made more advantageous than disadvantageous deck selections. Fellows and Farah (2005)

also found FTD patients IGT to be impaired compared to controls. They also suggest the reversal learning element in the original IGT to involve the OFC which is affected in FTD patients. Therefore in this study we will investigate IGT in FTD patients and expected impaired performance if FTD has affected the OFC.

1.6 MND and FTD co morbidity: affects on decision-making

Motor neuron disease (MND) is the all encompassing term for many diseases of the motor neurone including ALS. ALS is the most progressive form of MND characterised by both upper and lower motor neuron involvement but without cognitive impairment (Abrahams et al., 2000). Lower motor neurone involvement results in muscle weakening, wasting, cramping and stiffness whereas upper motor neurone involvement can result in dysarthia, dysphasia and aspiration difficulties (Wyss, Visco & Chimes, 2011).

However approximately 3-5% of ALS patients, can present with a cognitive and behavioural profile akin to FTD patients resulting in a subgroup classified as FTD-ALS (Kew & Leigh in Rosser, 1992). From a group of 100 ALS patients, one third was found to have word generation impairment and fulfil research criteria for FTD (Lomen-Hoerth et al., 2003). Similarly, from a group of 36 FTD patients, Lomen-Hoerth (2002) found 5 fulfilled criteria for definite ALS and 13 fulfilled criteria for possible ALS. FTD patients can present with motor impairment similar to that observed in MND patients, which seems to suggest a link between the two diseases (Neary et al., 1990). Neary, Snowden and Mann (2000) also state that FTD-ALS patients experience pathological changes relatively confined to the OFC and temporal cortices, again displaying commonalities between FTD and FTD-ALS patients.

Cognitive impairments evident in FTD-ALS are largely seen in the executive domain (Doherty et al., 2010, Abrahams et al., 2005). Abrahams and colleagues (2000, 2005) have identified specific executive dysfunction in ALS in the form of impaired written and spoken verbal fluency due to an impaired supervisory attentional system (SAS; Shallice, 1988). These deficits were observed even when the effect of motor skills and speech production impairments were controlled for. Patients were recorded as taking longer to think of each word than healthy controls. In addition to verbal fluency deficits, the latter study also observed emotional labilty at the time of interview. Massman and colleagues (1996) found problem -solving, attentional and mental control deficits in 35.6% of

their FTD-ALS patient sample. Neary, Snowden and Mann (2000) also outline impaired executive functioning in abstraction, planning, set shifting and organisational skills in FTD-ALS. Therefore, MND patients are included here to investigate whether patients would perform similarly to FTD patients on decision-making tasks, given that both groups experience executive dysfunction and display behavioural abnormalities commonly found in patients with frontal atrophy.

1.7 Alzheimer's Disease and decision-making

Alzheimer's disease (AD) is a neurodegenerative disease of insidious onset at approximately age 65, defined by the DSM-IV-TR as the presence memory impairment and cognitive impairment in one other domain that affects social functioning and activities of daily living. Dubois and colleagues (2007) outline pathological markers of AD as: widespread medial temporal lobe involvement early on evident from structural MRI, molecular changes in temporoparietal areas discovered by PET scans as well as cerebrospinal fluid biomarkers. Although temporoparietal areas are first affected, Reed and colleagues (2007) state that frontal areas are implicated in later stages. Therefore executive dysfunction, and by extensive decision-making impairments, can be affected in later stages of the disease.

Decision making in patients with mild dementia of the Alzheimer's type (DAT) has been investigated using the IGT (Sinz et al., 2008). Results show that DAT patients select disadvantageous decks more frequently than controls. Controls change their selection strategies as the task progresses. However DAT patients continue to select disadvantageous decks even late into the task. Sinz and colleagues also report DAT patients' more impulsive card selections, indicative of perhaps failure to identify patterns and learn from punishments. It is important to remember the strong learning element in performing the IGT which might place AD patients at a disadvantage given their memory impairment.

If IGT performance is interpreted as a reflection of OFC damage then it would suggest that AD patients may have pathology in this area. Van Hosen and colleagues (2000) found significant OFC damage in a study involving 13 brain donors with AD. Pathology found consists of widening sulci, atrophic gyri discolouration medially and posteriorly as well as neurofibrillary tangles in cortical layers III and V. Neurofibrillary tangles were also found in the posterior and medial dysgranular

orbitofrontal cortices. Therefore other areas would not receive input from the OFC and hence would also be adversely affected, including the striatum, basal forebrain and amygdala (Van Hosen, Parvizi & Chu, 2000). These areas together compile circuits through which information is passed as they work together to process stimuli (Hsu et al., 2005). Working memory deficits might restrict formulation of strategies and therefore the IGT may not be suitable for AD patients with severe dementia, as deficits in latter abilities would make interpretation of their risk-taking behaviour ambiguous if they were to continuously select the high wins/losses decks.

1.8 Study outline

In this study, decision-making and reversal learning processes will be investigated in three different patient groups: FTD, AD and MND. These patient groups may all, depending on their stage of illness, have frontal involvement and therefore executive functions may be impaired and by extension decision-making abilities. The OFC is known to be involved in reversal learning and decision-making (Bechara et al., 19994, Rolls et al., 2000) and the DLF is also implicated in decision-making (Fellows & Farah, 2003). Two versions on the IGT are used, the original (OIGT) and shuffled (SIGT), as the original contains a reversal learning element and the shuffled does not. Another more simplistic reversal learning task (Hornak et al., 2004) will also be administered. These tasks are specifically used to investigate whether decision-making in general, or simply its reversal learning element, is affected in these patients. A range of background measures will be used to gage participant's decision-making performance in relation to their general cognitive ability. Patient scores will be compared against a group of similarly aged and gender-matched healthy controls.

1.9 Hypotheses

FTD Patients

- OFC affected early in the disease with the DLF affected later
- FTD with OFC involvement: normal performance on the shuffled IGT but impaired performance on the original IGT and reversal learning task
- FTD with DLF involvement: normal performance on reversal learning task but impaired original and shuffled IGT performance

MND Patients

- MND often associated with FTD with evidence of similar impairments in executive functioning and behavioural changes
- Decision-making, as an aspect of executive functioning, may be impaired
- Normal performance on shuffled IGT but impaired original IGT and reversal learning performance if OFC is affected
- Impaired on original and shuffled IGT with normal performance on the reversal learning task if DLF is affected

AD Patients

- OFC not affected until much later in the course of the disease
- Normal performance on shuffled IGT but impaired original IGT and reversal learning performance if OFC is affected
- Impaired on original and shuffled IGT with normal performance on the reversal learning task if DLPFC is affected
- Performance similar to controls if patient does not yet have frontal involvement (in early stages of the disease)

2. Methodology

2.1 Participants

32 patients were contacted about the study, with 12 consenting to take part. 6 patients completed the battery, 4 partially completed the battery and 2 patients were not included. Data was unattainable in some cases due to the severity of patient conditions. 10 patients were included in

the study: 5 males and 5 females. Patients mean age was 63.4years/S.D. 4.993), mean education level was 11.8years/S.D 2.3 and Mini Mental State Examination score (MMSE; Folstein, Folstein & McHugh, 1975) mean score was 27/ S.D. 5.425. The patient sample consisted of three groups: 5 Motor neuron disease (MND), 4 Fronto-temporal dementia (FTD) and 1 Alzheimer's disease (AD) patients. Patients were recruited through a combination of methods. Firstly, AD and FTD patients were recruited through the study's access to the Scotland Dementia Clinical Research Network (SDCRN). Secondly, details of FTD and MND patients, who had been seen in the last 18months, were obtained through Dr. Sharon Abraham's clinical files from the Jardine clinic and Day Hospital in the Royal Edinburgh Hospital. Lastly, previous MND and AD participants of other studies in the Psychology Department, University of Edinburgh, were also contacted about their interest in taking part in further research. Patients received information sheets in the mail that outlined the study, what was required of them and what the test session would involve. Patients provided consent by posting back response slips in the provided stamped, addressed envelopes. Appointments were agreed over the phone, to take place at a time and place that suited patients. Patients were given the option to be seen in the Psychology Department or researchers could conduct home visits.

Controls were recruited using the Psychology Department control bank, as the study was granted ethical approval by the school of Philosophy, Psychology and Language studies, University of Edinburgh. Control participants were contact by email. Controls were tested in the department only. 9 healthy participants were recruited, 5 males and 4 females, mean age 61.56/S.D. 6.984, education level mean score 16.56/S.D 2.651 and MMSE mean score 30/S.D.000. Before testing commenced, they each completed the WAIS and WMS - III exclusion criteria (see appendix X).

2.2 Materials

2.2.1 Background Tests

Verbal fluency (Written; Thurstone & Thurstone, 1962, Spoken; Spreen & Straus, 1998)

Written verbal fluency was assessed by asking participants to write down as many words beginning with a certain letter in a given time period; 1) "S" for 5 minutes, 2) "C" for four minutes. Participants

were asked to write the words, in a column on the left hand side of the page and then to make another column in exactly the same way on the right hand side of the page, if needed. Participants were then asked to copy each word from the lists they had just generated. This was timed to control for speed of writing. Verbal fluency indices were generated using the formula: total allotted time minus time taken to copy, divided by number of words generated. A verbal fluency index was generated for both letters individually and then combined. This index provides an estimate of the time taken to generate each word.

Spoken verbal fluency was measured by the number of words generated in one minute using the letters “P”, “R” and “W”. Participant’s verbal fluency was recorded and, during a test interval, the word lists were typed up by the researcher. The typed list was presented and again the participant was asked to say the word list out loud and timed. This was timed, to control for time taken to say the word, rather than think of each word. Time taken to say the word list was deducted from 1 minute. The time difference, divided by the number of words generated, was used as the spoken verbal fluency index. Indices were calculated for each letter and then combined. Written and spoken verbal indices were each converted to z scores using the formula; patient or control score - control mean /standard deviation of control score.

Brixton Spatial Anticipation Test (Burgess& Shallice, 1996c)

A stimulus booklet consisting of 56 pages was presented. Each page contained an image of a horizontal rectangle with ten circles inside (two rows of five circles), each numbered. On every page, one of the circles was coloured blue. Participants were asked to guess where the blue circle would fall next. The coloured circle moved around as each paged was turned according to a pattern. The numbers referred to the position of the circle only, the task was not mathematical. Participants were asked to try and pick up on the pattern as quickly as they could by predicting where the coloured circle would fall next. Participants were told that the pattern would change intermittently and that they must try to pick up on the new pattern as quickly as they could. Reponses were considered correct if they followed the pattern. On pages where the pattern changed, the correct response was considered to be where the blue circle would have fallen, if the pattern had not changed. Raw scores reflect the total number of errors across the 55 page turns which are converted into standardised scores using the score sheet provided.

Wechsler Test of Adult Reading (WTAR; Wechsler, 2001)

The WTAR includes a list of 50 words that have atypical grapheme to phoneme translations, to read aloud. The words appear in order of increased difficulty and have irregular pronunciation, to minimize participant's application of standard pronunciation rules and to access their previous knowledge of the words. The test was not timed and participant's scores reflect the number of words correctly pronounced. Raw scores were converted into standardised scores using age and education tables provided in the WTAR scoring manual. The WTAR was used as measure of premorbid IQ for stored knowledge, such as, vocabulary and reading pronunciation skills.

Wechsler Abbreviated Scale of Intelligence (WASI; Wechsler, 1999)

Only the vocabulary and similarities subtests were used in this study as a measure of verbal intelligence alone was sufficient. For the vocabulary subtest, participants were asked to define 34 words. Participants were awarded 2 points if definitions were accurate, 1 if definitions were not quite accurate or simplistic and required further prompting or 0 if definitions were considered incorrect. For example, for the word lunch: 2 points awarded for afternoon meal/second meal of the day, 1 point awarded for meal/food and 0 points awarded for eat/nourishment.

The similarities subtest requires participants to explain the relationship between two words or the category to which both words belong, for 20 word pairs. For example, strawberries and grapes; 2 points awarded for accurate responses (fruits/berries), 1 point for vague responses (food/ have seeds) and 0 if responses are incorrect or too simplistic (both red/taste alike).

Total scores were converted to t scores, then combined and converted into a verbal IQ score using the tables provided in the WASI scoring manual.

Addenbrooke's Cognitive Examination- Revised (ACE-R; Mioshi et al., 2006)

The ACE-R measures 5 aspects of cognitive functioning: attention/orientation, memory, language, fluency, visuospatial capabilities. The ACE-R is used as a measure of cognitive performance and can be used to detect cognitive decline or as a measure of dementia severity after diagnosis, as well as differentiate between different types of dementia. Participants receive a score out of 100, which is a combined score from their performance on each of the aforementioned cognitive domains.

Visual Object and Space Perception Battery (VOSP; Warrington & James, 1991)

The VOSP cube analysis and number location subtests were used in this study to assess space perception. The cube analysis asks participants to count the number of 3-D cubes they can see in each picture, bearing in mind that cubes may be stacked one on top of another or be several cubes deep. The cube analysis has 2 practise trials and 10 real trials, giving a maximum score of 10. The number location task consists of two separate boxes on each page. One box contains a black dot, whilst the other contains numbers in a scattered presentation. The participant is required to match the number that corresponds to the position of the spot in the box below. The number location task consists of 2 practise and 10 real trials, with a maximum score of 10.

Graded Naming Test (GNT; McKenna & Warrington, 1983)

This task consists of 30 line drawings of objects that participants must name. The pictures increase with difficulty as the test progresses. The test is used as a measure of participant's naming abilities. Scores reflect number of correctly named drawings.

2.2.2 Questionnaires

Interpersonal Reactivity Index (IRI; Davis, 1980)

The interpersonal reactivity index is a 28 item questionnaire that measures both cognitive and emotional aspects of empathy. Each item is measured on a likert scale of A-E, where A = does not describe me/them well and E = describes me/them very well. The questionnaire has three different versions, one for the participant to rate themselves and two for their carers to rate the patient both currently and premorbidly. This is to account for the patient's potential lack of insight into their own behaviour. The IRI has four subscales with seven items on each: Perspective Taking (Item 8 "I try to look at everybody's side of the disagreement before I make a decision"), Fantasy (Item 12 "Becoming extremely involved in a good book or movie is somewhat rare for me"), Empathy Concern (Item 1 "I often have tender, concerned feelings for people less fortunate than I") and Personal Distress (Item 6 "In emergency situations, I feel apprehensive and ill-at-ease").

Each item is scored from 0-4, where A=0 and E=4, except for items 3, 4, 7, 12, 13, 14, 15, 18, 19 which were reverse scored due to negative phrasing; A=4 and E=0. Each subscale is scored out of a

possible 28 and combined to give a possible total score of 112. Total score gives an overall indication of a participant's degree of empathy, as measured by themselves or their carer where applicable. No cut-off scores were provided, therefore impairment was measured in comparison to controls.

Frontal Systems Behavioural Scale (FrSBe; Grace &Malloy, 2001)

The frontal systems behavioural scale is a 46 item rating scale used to measure behaviour in those with a neurological disorder to compare behaviour both before and after the onset of their illness. Responses are measured on a likert scale of 1-5, where 1= "almost never" and 5= "almost always". The FrSBe contains two columns, one marked before onset of illness and the other currently. The FrSBe has two versions, one for the patient and a second for their carer. Again this is to account for the patient's possible lack of insight into their own behaviour. The FrSBe consists of three subscales: apathy (Item 14 "Sits around doing nothing"), disinhibition (Item 10 "Does or says embarrassing things") and executive dysfunction (Item 5 "Mixes up a sequence, gets confused when doing several things in a row").

Items are scored from 1-5, where 1=1 and 5=5, except for items 33-46 which were reverse scored due to negative phrasing; 1=5 and 5=1. Apathy is scored from a possible 70, disinhibition from 75 and executive dysfunction from 85. Subscale scores are combined to give a total score out of a possible 230. Total scores were converted to t scores using tables of age and education provided in the FrSBe scoring manual. Total t scores were used as an indication of participant's frontal systems behavioural syndrome.

2.2.3 Experimental Tests

IOWA Gambling Test (IGT; Bechara et al., 1994)

The IOWA Gambling Test is a decision-making task and was conducted on a touch screen laptop in this study. Participants were presented with Figure 1 onscreen. Participants had $2000 to begin with and were instructed to try and win as much money as possible by selecting cards from any deck they wanted, for 100 card selections. The green bar at the top of the screen gets longer with each win and a smiley face appears together with an ascending tone. However, when participants lose money the green bar gets shorter until eventually a red bar may appear as they enter a negative amount of

money. During losses, a sad face appears and a descending tone occurs. Participants are not aware that two decks are considered advantageous and two are disadvantageous. Advantageous decks produce small wins, however their losses are also small, whereas disadvantageous decks produce large wins but even larger losses. Therefore the small wins/losses decks were more advantageous over time. Participants must discover this pattern if they are to remain “in the green” and make a profit. They are informed that some decks are worse than others and to try and stay away from the “bad decks”. Participants are also advised to treat the money in the task as if it were real and to make decisions as if using their own money. Two IGT versions were administered.

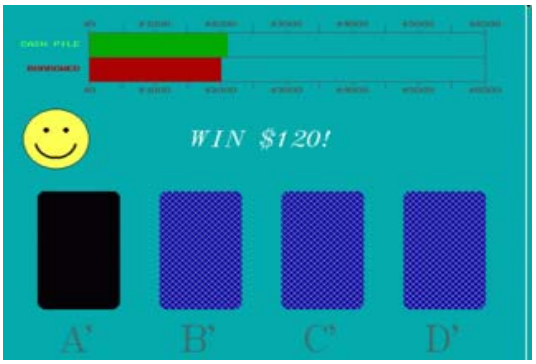


Figure 1: Iowa gambling task screen stimulus

IGT Original (OIGT): The first 8 cards of each deck are wins only, which typically results in participants selecting most cards from the high wins category initially. However, once punishments start to appear after the first 8 cards are selected, according to a schedule unbeknownst to participants, they will start to lose large amounts of money. This should result in participants reversing their initial strategy and realising that the low wins, low losses decks are more advantageous in the long run. As the original IGT involves decision-making guided by rewards and punishments as well as reversal learning, it is thought to tap both the DLPFC and the OFC (Fellows and Farah, 2005).

IGT Shuffled (SIGT): This version is exactly the same as the OIGT, except that the first 8 cards in each deck are removed and placed to the bottom of the deck. Therefore punishments appear immediately, according to a schedule unbeknownst to the participant. Therefore the SIGT does not

involve reversal learning, as participants lose money from the start and can therefore use one strategy throughout the task: to win as much money as possible by avoiding the riskier decks. Participants should realise relatively quickly that the low wins, low losses decks are more advantageous in the long run. The SIGT was always administered after the OIGT. As SIGT involves decision-making guided by rewards and punishments without reversal learning, it is thought to tap the DLPFC only (Fellow and Farah, 2005).

Reversal Learning Test (Hornak et al., 2004)

The reversal learning test is a decision-making task conducted using a touch screen laptop. Participants were presented with two abstract patterns (see figure 2). By selecting a pattern you can win or/and lose an amount of money. Participants are required to discover which pattern is the "good" pattern that has higher wins and lower loses and therefore advantageous. The "bad" pattern has higher loses than wins and is therefore disadvantageous. When money is won, the participant is told they have won X amount, a green pile of coins and a happy face appears as well an ascending tone. When money is lost the participant is told they have lost X amount, the green coins reduce or possibly become red, a sad face appears and a descending tone occurs. Participants were instructed to keep touching the "good" pattern once they had discovered which one it was through trial and error. However, participants were informed that the "good" and "bad" patterns would switch periodically without warning and they would need to rediscover which pattern was now the "good" one. Participants were informed that this "switch" may occur several times throughout the task. This requires participants to reverse their initial learning. Reversal learning is thought to tap the OFC (Hornak et al., 2004). Once the task was complete, a questionnaire was administered asking participants which information they used to keep track of the "good" pattern. The options included: amount of money won/or lost on each trial, win/loss on each trial regardless of amount, cumulative total, pile of coins in corner of screen, colours associated with coin pile, sounds and faces. Responses were recorded simply as yes/no, except for item: amount won of lost on each trial, which was recorded no, yes consistently or yes inconsistently.

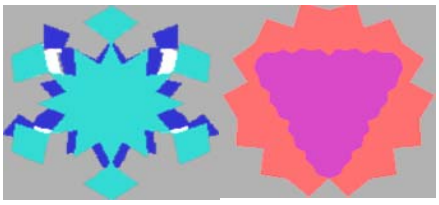


Figure 2. Reversal Learning Task screen stimulus

2.3 Procedure

The test session lasted approximately 4 hours. Control participants were seen in one test session in the Psychology Department in 7 George Square, University of Edinburgh. Patients were given the option of coming to the department or researchers visiting them in their homes. In either case, written informed consent was procured before testing began. Tests were administered at a table with the participant on one side and both researchers seated on the other, in a quiet setting without distraction. Tests were administered according to a set order (please see appendix A), although the order was flexible to patients needs or preferences. Computerised tests were intermixed with pen and paper tests so that the test session would be relatively varied for participants and give them a break from using the computer. Participants were allowed to take breaks when needed throughout the test session. Testing was administered in two separate test sessions where needed, to prevent patients from becoming tired or distressed. Whilst patients were engaged in tests, the free research assistant would administer questionnaires with the carer in a separate room. All participants were thanked for their time and participation once the test session was complete.

2.4 Statistical Analysis

Tests were scored according to their provided scoring manuals. Results were entered and analysed using SPSS (Chicago Inc, 1999). Patient performances were analysed using nonparametric methods as assumptions of normality were violated due to small and unequal sample size between patient groups. Kruskal Wallis H tests were used to investigate between group differences. Significant findings were further investigated using Mann Whitney U tests and medians were used as an indication of patient performance. Correlations were also used to investigate relationships between

different measures using Spearman's rho. Single case analysis was used to compare individual patient's performance to that of the other patients and control means using the computer program Singlims_ES.exe (Crawford, Garthwaite & Porter, 2010). Dissociations between patient scores on two tasks compared to control means were investigated using the computer program RSDT_ES.exe (Crawford, Garthwaite & Porter, 2010).

2.5 Ethics

The study was granted approval by the school of Philosophy, Psychology and Language Studies, University of Edinburgh and the Lothian Research Ethics Committee. Participants signed an informed consent form prior to their participation, as did their carers where attainable (See Appendix B for e.g. Consent Form).

3. Analysis

Nonparametric analysis was used in this study as the assumptions of normality were violated due to small sample size and uneven number of participants per group. Data missing in parts due to collection difficulties and severity of patient illness.

3.1 Background Measures

There was a significant between group difference (FTD *n*= 3, MND *n*=4, Controls *n*=9) in participants' ACE-R scores as revealed using a Kruskal Wallis H test (*H* (2) = 12.128, *p* <.05). A Mann Whitey U test revealed FTD patients (*Md*= 82) had significantly lower ACE-R scores than controls (*Md*= 99), U= .000, *z*= -2.550, one-tailed *p* <.05, *r*= .7. A second Mann Whitney T test revealed a significant difference between MND patient scores (*Md*= 93) and controls (*Md*= 99), *U*= .000, *z*= -2.824, *p*<.05, *r*= .7. Using single case analysis (Crawford, Garthwaite & Porter, 2010) the AD patient's ACE-R scores was significantly below that of the controls (*p*<.05). In total 5 patients were below the cut-off of <~88 and 3 were below <~82 from a total of 8 patients who completed the ACE-R (see Table 1). Scores below 88 on the ACE-R are 94% sensitive and 89% specific for dementia, whereas scores below 82 are 84% sensitive and 100% specific for dementia.

Kruskal Wallis H test also showed significant between group differences (FTD *n*= 3, MND *n*=5, Controls *n* =8) on the Brixton Test of Spatial Anticipation using the standardised scores (*H* (2) = 9.231, *p*<.05). Post hoc comparisons using Mann Whitney U tests showed FTD patients (*Md*=1) to score significantly lower than controls (*Md*=7), *U*= 1.500, *z*= -2.210, one-tailed *p*<.05, *r*= .7. A second Mann Whitey U test revealed significant differences between MND patients (*Md*=2) and controls (*Md*= 7), *U*=3, *z*=-2.582, *p*<.05, *r*=.7.

Z score conversions of spoken verbal fluency indices demonstrated significant between group differences (FTD *n*= 3, MND *n*=5 and Controls *n*=9) using a Kruskal Wallis H test (*H* (2) = 11.671, *p*<.05). A Mann Whitney U tests showed FTD patients (*Md*= 6.57) to have significantly higher spoken verbal fluency z scores than controls (*Md*= -.09), *U*= .000, *z*= -2.501, one-tailed *p*<.05, r= .7, and MND

patients (*Md*= 2.83) to have significantly higher spoken verbal fluency z scores than controls (*Md*= -.09), *U*=1, *z*= 2.87, *p*<.05, *r*=.7. Using single case analysis, the AD patient was also found to have a significantly higher spoken verbal fluency z score than controls when *p*<.05 (see Table 1 for individual patient scores). Higher z scores for spoken verbal fluency indicate a longer time to generate each word, when speech impairments were controlled for.

Written verbal fluency index z scores were not found to have significant between group differences using a Kruskal Wallis H test (p=.267). Significant deficits were found using single case analysis (see Table 1).

Lastly, between group differences (FTD *n*=3, MND *n*=5, Controls *n*=9) were found for WTAR standardized scores (*H* (2) = 9.574, *p*<.05). However, a Mann Whitney did not reveal significantly lower FTD or MND scores than controls (*p*= 1). There was a significant difference between MND (*Md*= 101) and controls (*Md*=119), *U*=5, *z*= 2.946, *p*<.05, *r*=.7.

WASI vocabulary (*p*=.363) and WASI similarities (*p*=.063) t scores, WASI verbal intelligence scores (*p*=.252), as well as Graded Naming Test (*p*=.337) and VOSP number location (*p*=.283) and cube analysis (*p*=.866) scores, were not found to produce significant between group differences using the Kruskal Wallis H test.

Single case analysis was conducted using the Singlims_ES.exe computer program (Crawford, Garthwaite & Porter, 2010) to investigate possible significant differences between patient and control scores on background measures that might not have been detected by Kruskal Wallis H tests. Results are displayed in Table 1.

Table 1

Background Measures	**1**	**2**	**8**	**9**	**10**	**11**	**12**	**16**	**17**	**25**	**Case ID Numbers**
Patient Type	FTD	FTD	MND	MND	MND	MND	MND	FTD	FTD	AD	Controls(n=9) mean score
ACE-R	53*	82*	95*	96*	91*		88*		88*	51*	98.78
Score <88; 94% sensitive & 89% specific for dementia											
Executive Functions											
Brixton Standardized Score	1*	6	6	2*	2*	2*	6		1*		7.25
Written Verbal Fluency Z score		1.92	1.26			0.79			-0.43	10.35*	0.0022
Spoken Verbal Fluency Z score	12.61*	6.57*	2.4*	1.58	2.83*	4.03*	3.9*		1.85	11.1*	0.0033
Verbal Intelligence/Language Abilities											
WASI Vocab T score		53*	59		61		59		69		62.44
WASI Similarities T score		56	49*		54		56		64		60
WASI Verbal IQ score		107*	106*		115		111		129		118.11
WTAR Standardized score	66*	113*	115	101*	106*	93*	101*		119		119.33

GNT	12	24	28	27	26	16	28	27	24.67
Visuospatial Abilities									
VOSP Number Location	1*	10	10	8	10		10	5*	9.11
VOSP Cube Analysis	0*	10	10	9	10		10	10	9.56

Patient Individual Performance scores on background measures compared to control mean scores

*Significant p<.05

Missing data due severity of patient illness

A Kruskal Wallis H test failed to produce a significant difference between patient groups (FTD *n*=2, MND *n*=4) on the before self rated FrSBe questionnaire total t score (*p*=.643). Group differences were not found on the after self rated FrSBe questionnaire total t score either (*p*=.343).

Kruskal Wallis H test did not find a significant difference between groups (FTD *n*=3, MND *n*=4) on the before family rated FrSBe questionnaire using total t scores (*p*=.077). However, a significant was found using total t scores on the after family rated FrSBe questionnaire (H (1) = 4.582, p <.05). A Mann Whitney U test revealed FTD patients to have significantly higher scores total t scores (*Md*= 108) compared to MND patients (*Md* 60), U= .000, z= -2.141, p<.05, r=.8. Controls did not complete family rated FrSBe questionnaires for obvious reasons.

As individual group scores on different rating scales cannot be compared to one another statistically using nonparametric analyses, mean scores for each group were plotted using histograms to display differences between patients before and after scores, and patients versus carer scores.

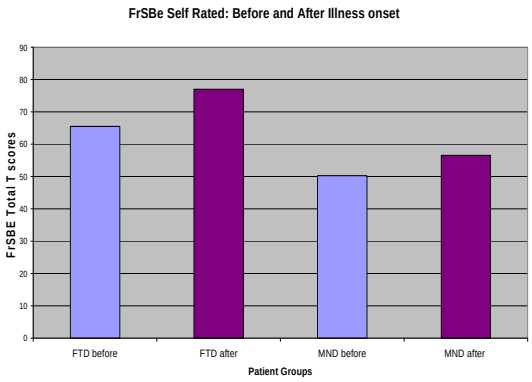


Figure 1. FrSBe Self Rated: Before V After

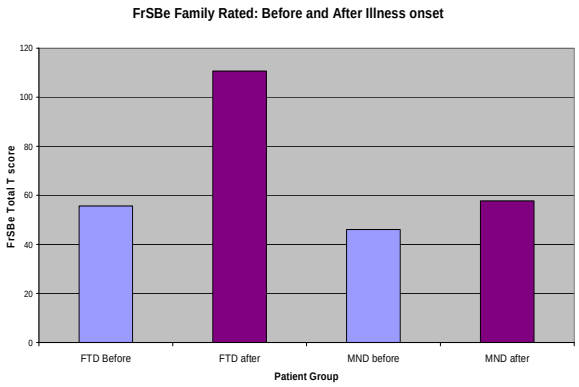
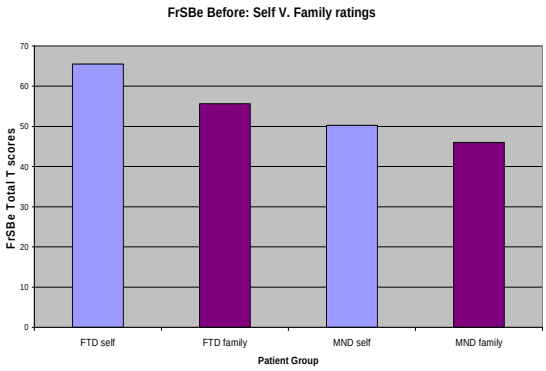


Figure 2. FrSBe Family Rated: Before V After



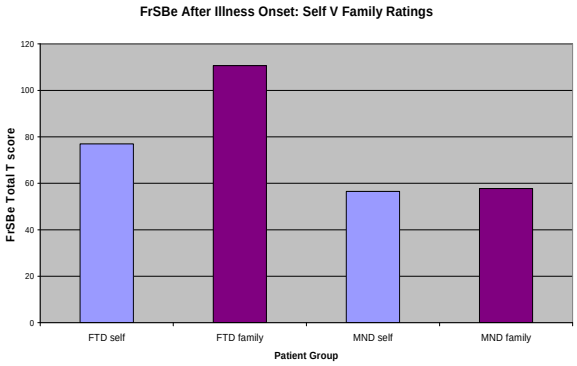


Figure 3. FrSBe Before: Self V Family Ratings Figure 4. FrSBe After: Self V Family Ratings

Kruskal Wallis H test failed to reveal any between group differences for patients (FTD *n*=2, MND *n*=4) on the before self rated FrSBe questionnaire for subscale t scores: apathy (*p*=.643), disinhibition (*p*= .643) or executive dysfunction (*p*=. 165). Similarly, no group differences were found on the after self rated FrSBe questionnaire for any of the subscale t scores: apathy (*p*=.089), disinhibition (*p*= .682) or executive dysfunction (*p*=.257).

Between group differences (FTD *n*=3, MND *n*=4) were found on the before family rated FrSBe questionnaire using a Kruskal Wallis H test (*H* (1) = 4.582, *p* <.05) for subscale t scores: disinhibition. A Mann Whitney U tests revealed FTD patients (Md= 48) to have significantly higher disinhibition t scores than MND patients (*Md*= 40.5), *U*= .000*, z*= -2.141, *p*<.05, *r*=.8. Between group differences were also found on the after family rated FrSBe questionnaire on subscale t scores disinhibition (*H* (1) = 4.5, *p* < .05) and executive dysfunction (*H* (1) = 4.5, *p* < .05). A Mann Whitey U test displayed FTD patients to have significantly higher disinhibition t scores (*Md*= 92) than MND patients (*Md*= 46), *U*.000, *z*= -2.121, *r*= .8. A second Mann Whitney U test displayed FTD patients to have significantly higher executive dysfunction t scores (*Md*= 107) than MND patients (*Md*= 53.5), *U*= .000, *z*= -2.121, p<.05, *r*= .8.

Single case analysis revealed significant deficits for some patient's individual scores. Results below 65 are below the cut-off for impairment according to the FrSBe scoring manual

FrSBe Before Total T scores	1	2	8	9	10	12	16	17	25	**CaseID**

Table 2.

FrSBe Before Scores: Comparison of single case total T scores between self and family ratings (case ID used)

Patient Type	FTD	FTD	MND	MND	MND	MND	FTD	FTD	AD
Self Rating Total T Scores		86*	47	48	40	66*		45	
Family Rating Total T scores	61	48	46	49	47	42	58		50

FrSBe After Total T scores	**1**	**2**	**8**	**9**	**10**	**12**	**16**	**17**	**25**	**CaseID**
Patient Type	FTD	FTD	MND	MND	MND	MND	FTD	FTD	AD	
Self Rating Total T Scores		99*	54	60	38	74*		55		
Family Rating Total T scores	125*	108*	64	64	47	56	99*		83*	

* Below cut-off >65

Missing data due to collection difficulties

Table 3.

FrSBe After scores: Comparison of single case Total T scores between self and family (case ID used)

* Below cut-off >65

Missing data due to collection difficulties

Kruskal Wallis H test did no find any significant differences between groups on either the self IRI (FTD *n*=2, MND *n*=3, Controls *n*=9, *p*= .961) or current IRI (FTD *n*=3, MND *n*=3, *p*=.127). However a

significant difference was found between groups (FTD *n*=3, MND *n*=3) on the premorbid IRI (*H* (1) = 2.857, *p*<.05). A Mann Whitney U test revealed FTD to have significantly lower score *(Md*= 44) than MND patients (*Md*= 59), *U*= .000, *z*=-1.964, *p*<.05, *r*=.8.

A Kruskal Wallis H test did not reveal and between groups differences (FTD *n*=2, MND *n*=3, Controls *n*=9) on the self IRI for subscales: perspective taking (*p*= .414), fantasy (*p* =.95), empathic concern (*p* =.964), personal distress (*p* =.329). No group differences (FTD *n*=3, MND *n*=3) were found on the current IRI for any subscales (*p* =.268, *p*=.5, *p* =.513, *p* =.275). Lastly no between group differences (FTD *n*=3, MND *n*=3) were found on the premorbid IRI for any subscale (*p* =.268, *p* =.827, *p* =.658, *p* =. 275).

As differences between separate measures in a single patient group cannot be investigated using nonparametric analysis, differences between carer premorbid and current ratings, as well as patient and carers ratings will be displayed using group mean scores on histograms. Controls mean scores will also be displayed with which patient performance can be visually compared.

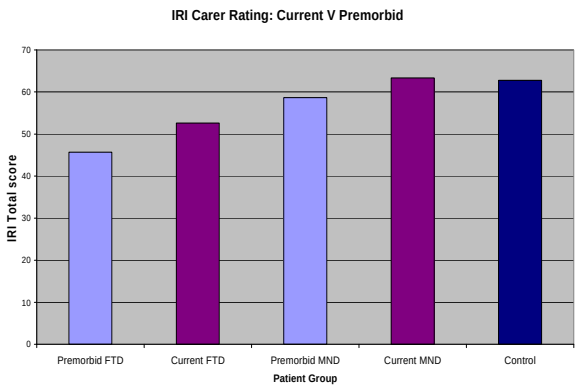


Figure 5. IRI carer ratings: Current V Premorbid

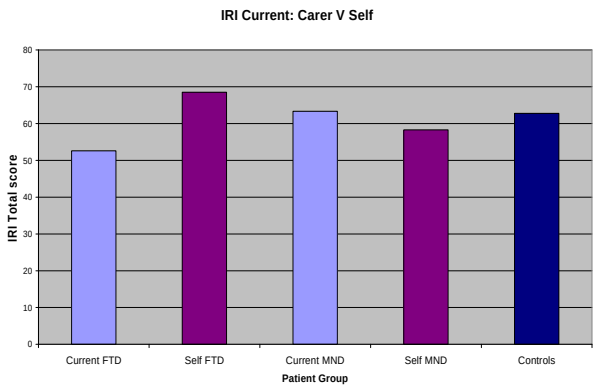


Figure 6. IRI current ratings: Carer V Self

Single case analysis was used to compare patient's scores to controls mean scores on the self IRI as there were no cut-off scores provided for the IRI total scores, see Table 4 below for results.

Table4.

IRI Total scores compared to control mean on self rated version (patients referred to using case ID)

* Significant P<.05

Missing data due to severity of patient's illness

3.2 Experimental Tasks

3.2.1 Original Iowa Gambling Task (OIGT)

No group differences were found between FTD (*n*=4), MND (*n*=5) and controls (*n*=8) for the total

IRI Total Scores	1	2	8	9	10	12	16	17	25	**Case ID**
Patinet Type	FTD	FTD	MND	MND	MND	MND	FTD	FTD	AD	Controls(n=9) mean score
Self Rated		60	80		21*	74		77		62.78
Carer Rated Premorbid	61	48	69	64	57		49		40	62.78
Carer Rated Current	40	53	59	56	61		44		68	62.78

number of advantageous deck selections made over 100 trials according to the Kruskal Wallis H Test (p=.128).

Deck selections were then analysed in 5 blocks, with 20 card selections in each. Performance was measured using the total number of cards selected from advantageous decks in each block (maximum = 20). Again, using Kruskal Wallis, a significant difference was found between groups on block 3 (H (2) = 8.414, p<.05). Mann Whitey U test revealed FTD (Md=9) to have a significantly lower difference score for block 3 than controls (Md= 13.5), U=1.00, z= -2.575, one-tailed p<.05. r=.7. Hence FTD patients selected significantly less cards from advantageous decks than controls did on

block 3. MND patients were not significantly impaired on block 3 (p=.524). No other block was found to produce significant between group differences. Figure 1 depicts block group differences in the OIGT performance.

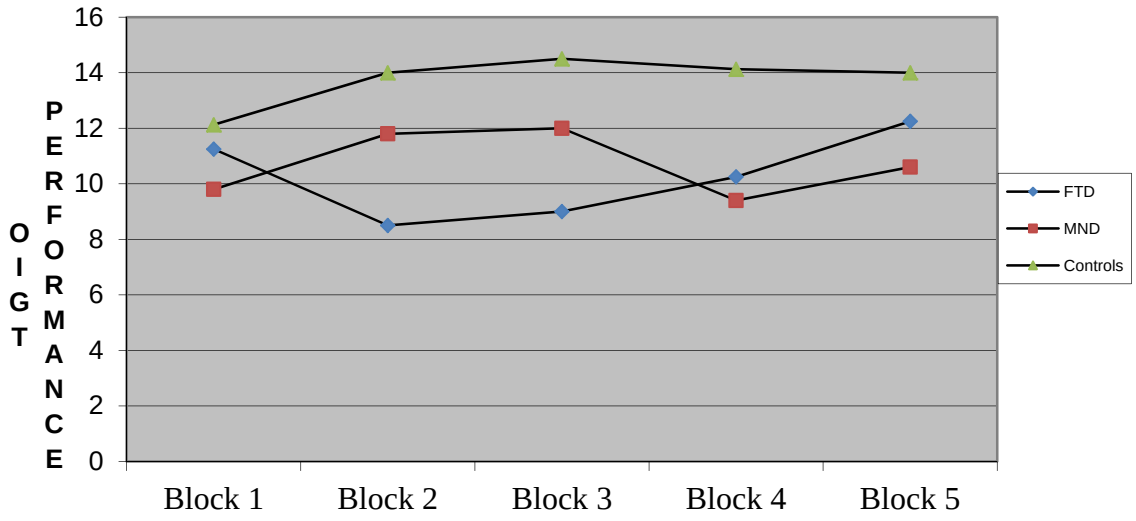


Figure 7 Mean performance on the OIGT for FTD, MND and controls. The graph illustrates the mean number of advantageous deck selections per patient group made over 5 blocks of 20 trials per block.

Single case analysis did not reveal any individual differences in the total number of cards selected from advantageous decks over 100 trials per patient compared to the control mean score. However, as Table 2 displays, most patients did choose fewer cards from the advantageous decks than controls, even if this difference was not proven to be significant. Even when trials were divided into 5 blocks, of 20 trials per block, no significant differences were found between individual patients and controls. Table 2 also displays patient's generally lower number of advantageous deck selections over 5 trial blocks.

OIGT	**1**	**2**	**8**	**9**	**10**	**11**	**12**	**16**	**17**	**Case ID**
Patient Type	FTD	FTD	MND	MND	MND	MND	MND	FTD	FTD	**Control (n=8)**
Total Advantageous Deck Selections (100 trials)	49	53	69	52	58	44	44	50	53	68.75
Trial Blocks (20 trials)										
Block 1	11	9	11	9	12	8	9	9	16	12.125
Block 2	8	11	12	10	17	13	7	10	5	14
Block 3	8	10	15	11	12	11	11	9	9	14.5
Block 4	12	9	16	11	7	7	6	11	9	14.125
Block 5	10	14	16	11	10	5	11	11	14	14

Table 5

Patient performance on OIGT: Number of Advantageous Decks Selected in Total (100 trials) and over 5 Blocks (20 trials)

3.2.2 Shuffled Iowa Gambling Task (SIGT)

A Kruskal Wallis revealed a significant difference (FTD *n*=3, MND *n*=4, Controls *n*=7) between the groups on total advantageous deck selections (H (2) = 7.907, p<.05) for the shuffled variant of the IGT. A Mann Whitney displayed that the FTD patients (*Md*= 53) selected significantly less cards from the advantageous decks than the controls (*Md*= 87), U= .000, z= -2.393, one-tailed p<.05 r= .7 MND patients were also selected significantly less advantageous cards (*Md*= 60) than controls (*Md*= 87), U=3, z= -2.079, p<.05, r= .6. The AD patient was also found to be significantly impaired using single case analysis (p<.05).

Kruskal Wallis H tests were run on each block and a significant between group differences was found for block 5 (H (2) = 7.892, p<.05). A Mann Whitney demonstrated that the FTD patients (Md= 8) selected significantly less cards from the advantageous decks in block 5 than controls (Md= 19), U= .500, z= -2.3, one-tailed p<.05, r= .7. MND patients were also significantly impaired (Md= 9) on block 5 compared to controls (Md= 19), U= 2.5, z= -2.193, p<.05, r=.6. However the AD patient was not found to be impaired on block 5 compared to controls using single case analysis (p=.117). Figure 2 depicts differences in group SIGT block performance.

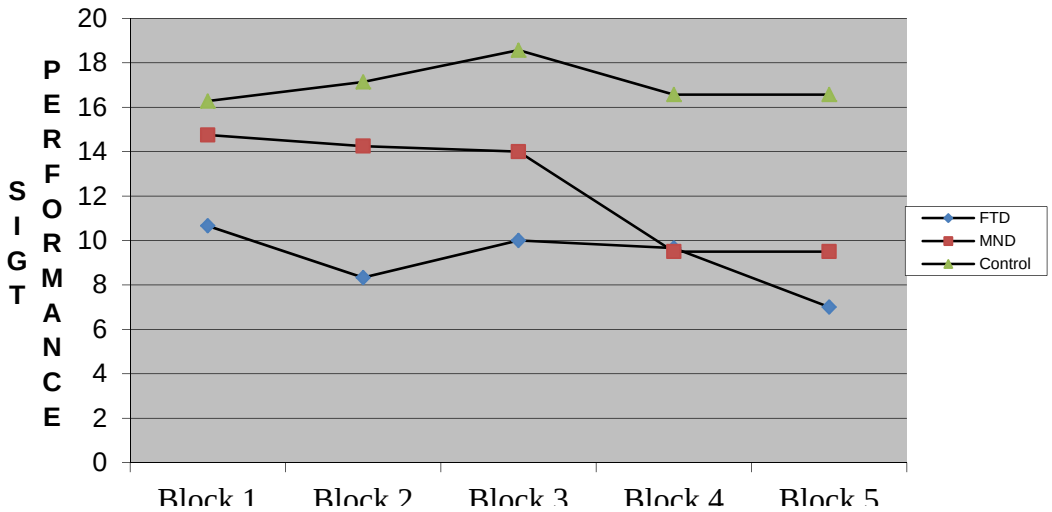


Figure 8 Mean performances on the SIGT for FTD, MND and controls. The graph represents the mean number of advantageous card selections per group, over 5 blocks with 20 trials per block.

Single case analysis of patient's individual performance revealed that 6 out of 8 patients selected significantly less cards from advantageous decks over 100 trials on the SIGT. Patient's SIGT block performance is also shown in Table 3, with many patients selecting significantly less cards from the advantageous decks than controls in each block except in block 4. No patient selected significantly less cards from advantageous decks than controls in block 4.

Table 6

Single Case Analysis of Patient's SIGT Performance: Total and Block Advantageous Deck Selections

SIGT									
	1	**2**	**8**	**9**	**10**	**12**	**17**	**25**	**Case ID**
Patient Type	FTD	FTD	MND	MND	MND	MND	FTD	AD	Control (n=7) mean score
Total Advantageous Deck Selections (100trials)	21*	57*	69	51*	44*	84	53*	60*	85.71
Trial Blocks (20 trials)									
Block 1	7*	12*	18	10*	14	17	13	8*	16.2857
Block 2	0*	12	19	13	9*	16	13	13	17.1429
Block 3	0*	12*	20	12*	6*	18	18	16	18.5714
Block 4	9	11	7	7	6	18	9	12	12.5714
Block 5	8*	10	5*	9	9	15	4*	11	16.5714

*One-tailed significance p<.05

Using single case analysis, dissociations between patient's OIGT and SIGT performance were investigated in comparison to controls using the RSDT_ES.exe computer program (Crawford, Garthwaite & Porter, 2010). OIGT performance was predicted to dissociate from SIGT performance, as the OIGT has a reversal learning element whereas the SIGT does not. The total number of advantageous deck selections over 100 trials was used as a measure of overall task performance for each task. Patient 1, 9, 10 and 17 (case ID) had significantly difference OIGT and SIGT performance when compared to control mean scores (one-tailed $p<.05$). Figure 3 displays patients' performance on both the OIGT and the SIGT, measured by the total number of advantageous deck selections made over 100 trials.

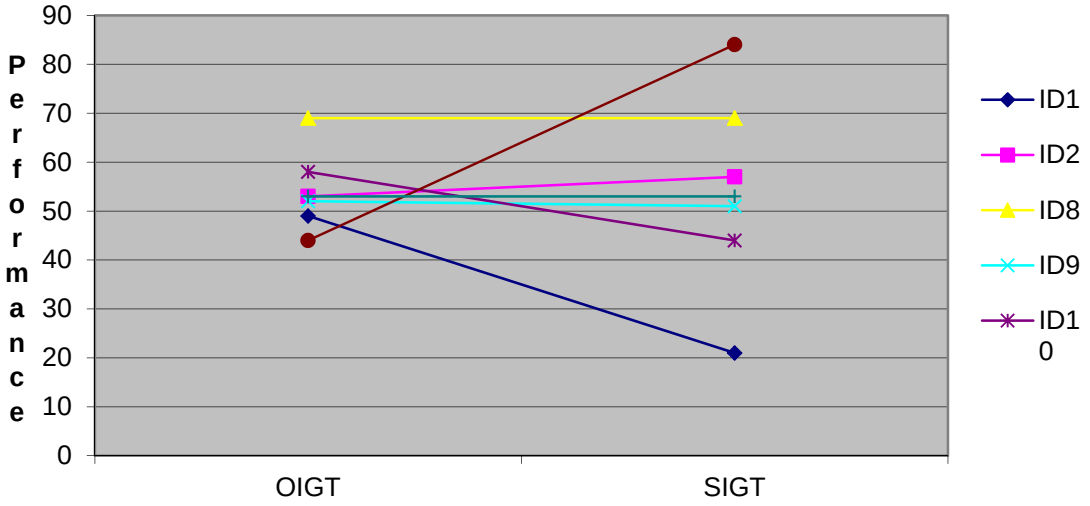


Figure 9 Individual patient scores on the OIGT and SIGT as measured by the total number of advantageous deck selections made on each task over 100 trials. Patients 1, 9, 10 and 17 had significant dissociations between task performance score when compared to control mean scores.

3.2.3 Reversal Learning Task

The reversal learning task proved to have no significant difference between groups (FTD *n*=2, MND *n*=4, Controls *n*=8), regarding the number of correct responses until the first switch of the task (*p*=.266) or the number of correct responses after the first switch (*p*=.476). Similarly, there were no between group differences on the numbers of switches that occurred in the task (*p*=.174). Switches represent participant's ability to reach criteria in selecting a certain number of correct responses in a row, displaying that they have learned and hence a switch (reversal) occurs. Again, there was no between group differences on percentage accuracy (*p*=.782) or the amount of money won at the end of the task (*p*=.611). Whether participants paid attention to the salient on-screen stimuli, as indicated on the post-test questionnaire, also did not result in any between group differences

.

Single case analysis did not show any significant deficits for individual patient scores on any of the reversal learning task variables. However, inspection of patient individual scores does show that many are lower than controls, see Table 4.

Table 6

Patient score for variables on the Reversal Learning task.

Reversal Learning Task	**1**	**8**	**9**	**10**	**12**	**17**	**25**	**Case ID**
Patient Type	FTD	FTD	MND	MND	MND	FTD	AD	Control (n=8)mean score
Amount of Money	-6924	-2376	-12491	-3933	-1190	-6155	-7980	-2247.5
Amount of Switches	2	3	4	3	5	2	3	4.5
Hits until Switch 1	12	9	9	9	10	15	9	16.38
Hits after Switch 1	44	49	56	52	55	43	40	46
Percentage Accuracy	53.7	55.7	61.5	57.1	62.5	58.1	44.4	60.26
Salient Stimuli	2	2	1	2	3	2	1	1

Correlation analyses were conducted between reversal learning performance (percentage accuracy) and OIGT performance (total number of advantageous decks selected out of 100 possible trials i.e. percentage accuracy) using Spearman's rho, as both tasks are thought to involve the OFC. There was a moderate positive relationship between the two variables (r=.454, n= 13) that explained 20.6% of the variance. However the correlation was not significant (p= .119). Unexpectedly, there was a significant, strong, positive relationship between reversal learning and SIGT performance (r= .587, n= 12, p<.05). The correlation here explained 34.45% of the variance between the two variables. Therefore high accuracy on the reversal learning task was associated with high performance levels on the SIGT. Lastly, there was a strong significant positive relationship between OIGT and SIGT performance (r=.544, n= 14, p<.05), explaining 29.5% of the variance. Therefore high accuracy on the OIGT was associated with high accuracy on the SIGT.

4. Discussion

4.1 Main Findings

This study sought to investigate complex decision-making making under ambiguity in patients with FTD, MND and AD. Also under investigation was the possible contribution of reversal learning to processes of decision-making. Missing data was the result of data collection difficulties due to the severity of patient's illnesses and hence their level of ability. The main findings of the study were: 1) there were no group or single case differences for patient's performance on the OIGT over 100 trials, however analysis of 20 trial blocks did reveal significantly different group performances between FTD and MND patients compared to controls, 2) there were significant group and single case differences on the SIGT for all patient groups compared to controls in both total and block analysis, 3) there were no significant group or single case differences between patients and controls in performance on the reversal learning task, however inspection of individual scores does reveal lower scores for patients compared to controls even if these differences were not statistically significant, 4) OIGT was found to significantly dissociate from SIGT performance in a number of patients using single case analysis, 5) lastly reversal learning performance did not significantly correlate with OIGT performance, but unexpectedly did significantly correlate with SIGT performance, as did OIGT and SIGT performance.

4.2 IGT findings and implications

In contrast to (Fellows & Farah, 2005**),** this study did not find significant group or single case differences between patients and controls on the OIGT as measured by the total number of advantageous deck selections made over 100 trials. However, figure 1 displays each patient group's performance over 5 blocks of 20 trials per block to investigate patient's performance patterns throughout the task that may not be evident from viewing the total scores alone. Block analysis did reveal significant differences between FTD patients and controls as well as between MND patients and controls in block 3. Therefore in block 3 FTD and MND patients selected significantly less cards from advantageous decks than controls. Fellows and Farah (2005) found patients with OFC lesions to be impaired on the OIGT due to its reversal learning element. The OFC is believed to be involved in reversal learning (Rolls et al., 2000).

The OIGT involves reversal learning, as patients must reverse their initial strategy. To begin with, participants select the high wins/losses decks. However as losses start to appear, participants learn that the low wins/losses decks are more advantageous overall and hence reverse their initial strategy. As the OFC is known to be implicated in FTD (Doherty et al., 2011), this finding was

expected. MND impaired performance was also hypothesised, if the OFC was involved. The OFC can be affected in MND (Neary, Snowden & Mann, 2000), with 3-4% of MND patients experience cognitive and behavioural deficits characteristic of FTD (Kew & Leigh in Rosser, 1992).

Figure 7 displays OIGT performance for FTD, MND and controls, as measured by their group mean score for the number of advantageous deck selections made over 5 blocks. Controls chose more advantageous decks in block 2 than block 1, indicating that they successfully reversed their initial strategy. Control performance stayed consistent from block 2 to 5, as they continued to select predominantly advantageous decks throughout the rest of the task. As discussed, FTD performance was the most impaired, with patients selecting predominantly disadvantageous decks throughout the task. In fact, FTD patients did not select more advantageous than disadvantageous decks in any trial block. MND patients reversed their initial strategy after block 1 and proceeded to select predominantly advantageous decks throughout blocks 2 and 3. However in block 4 and 5, their performance disimproved to that of FTD patients.

Reasons for this sudden drop in performance for MND patients may be due to executive dysfunction. Neary, Snowden and Mann (2000) outline executive functioning impairments in FTD-ALS patients in terms of abstraction, planning, set shifting and organisational skills. MND patient in this study demonstrated deficits in the background executive functioning tasks with 4 out of 5 MND patients revealing significantly impaired spoken verbal fluency indexes (Abrahams et al., 2000) and 3 out of 5 patients revealing significantly impaired performances on the Brixton spatial anticipation task (Burgess & Shallice, 1996c). Abrahams and colleagues (2005) also found MND patients to have executive impairment as measured by spoken and written verbal fluency even when speech and writing disabilities were controlled for. In tasks of design fluency, patients with MND were thought to be unable to override inappropriate responses and therefore generated more unacceptable drawing than controls (Abrahams et al., 2000). This inability to override inappropriate responses was suggested to be a result of an impaired supervisory attentional system (SAS; Shallice, 1988). Therefore it is possible that MND patients reverted back to their initial strategy, selecting the high wins/losses decks, in blocks 4 and 5 as they could not override the inappropriate response due to SAS failure.

Results from the SIGT revealed FTD, MND and AD patients to be significantly impaired compared to controls on the total number of advantageous decks selected over 100 trials. This finding was somewhat unexpected as the SIGT does not have a reversal learning element. However Fellows and Farah (2005) found patients with DLF lesions to be deficient on both the OIGT and the SIGT. FTD pathology starts in the OFC and cingulate cortices initially and then becomes widespread throughout the frontal lobe as the disease progresses (Doherty et al., 2011). Therefore SIGT impaired performance may be due to DLF involvement as patients may be in later stages of the disease. However this still does not entirely explain why FTD patients were not impaired on the OIGT as the OFC would still be affected as well as the DLF. A possible reason may by that control performance was not high enough to produce significant differences between FTD and control performances. Fellows and Farah (2005) found that their patients with VMF lesions did not display as impaired a performance as the patients did in Bechara's study (1994). Therefore, perhaps FTD patient's performance in this study was even less disadvantageous than MNF lesions in the Fellows and Farah study (2005).

Similarly MND patients may also be impaired on the SIGT, as the frontal lobe can be affected (Neary, Snowden & Mann, 2000). As Reed and colleagues (2007) state that the frontal lobe is affected in later stages of AD. Neurofibrillary tangles were also found in the medial and posterior parts of the OFC in all 13 AD brain donors in a study by Van Hoesen, Parvizi and Chu (2000). As the patients had an ACE-R score of 51, it can be conceded that they were profoundly demented and therefore it is likely that the OFC was affected. These results may explain the AD patient's impaired SIGT performance

SIGT block analysis demonstrated significant group differences between FTD and MND patients and controls in block 5 only. FTD performance disimproved progressively throughout the entire task, however it was not until block 5 that these differences became statistically significant. MND patients selected predominantly advantageous decks through blocks 1-3, however performance again drops drastically in blocks 4 and 5. Patients were impaired on this task possibly due DLPFC involvement which has been related to working memory impairments (Fellows & Farah, 2003).The possibility of frontal involvement in each patient group, depending on their stage of illness, has been established. Impaired performance reflects failure to attend appropriately to reward and punishment feedback. FTD is known to cause disinhibition and impulsivity making continuous selection of the high

wins/losses decks not surprising. Rahmann and colleague (1999) also identified FTD patients to be "risk takers" in the Cambridge gambling task. As stated earlier, approximately 3-5% of ALS patients can present with a cognitive and behavioural profile akin to FTD patients. Therefore it is possible that the MND patients also experience disinhibition and impulsivity that impairs their responses to reward and punishment feedback in the SIGT.

Figure 2 displays all group performances across 5 trial blocks. Controls selected between 16-19 cards on average from advantageous decks in every trail block throughout the whole task. Therefore controls learned quickly that the low wins/losses decks were more advantageous in the long run and responded appropriately to the rewards and punishments as they occurred. FTD patients selected more disadvantageous decks than disadvantageous decks in every trial throughout the task. MND patients initially selected cards predominantly from the advantageous decks. However after block 1, patient performance disimproved progressively from block 2 until the end of the task. Perhaps as mentioned with the OIGT, MND patients could not maintain their initial strategy over a prolonged period which may be a result of their impaired executive functions. Another possibility for their performance may be due disinhibition and risk-seeking behaviours characteristic of frontal lobe involvement. As in the OIGT, MND patient performance took a considerable disimprovement in block 4. It is possible that due to some attentional deficits related to their executive dysfunction, that MND patients fail to maintain their initial strategies in latter stages of decision-making.

In contrast, single case analysis demonstrates that the AD patient was significantly impaired in block one only, even though their performance was low throughout the task (AD performance was significantly impaired performance over 100 trials). This suggests that the AD patient did not maintain an advantageous strategy throughout the task and hence made erratic choices.

A significant dissociation was found between OIGT and SIGT performance. This was expected due to the reversal learning element in the OIGT. However the direction of the dissociation was unexpected as SIGT performance was more impaired than OIGT. It was hypothesised that OIGT would be more impaired due to expected OFC involvement in patient groups and its role in reversal learning. This suggests that patients may have greater involvement in the DLPFC as this area is associated with impairment on both the OIGT and SIGT.

4.3 Reversal learning task results and implications

To further investigate whether reversal learning was impaired a more basic task was administered (Bechara et al., 1994). However both group and single case analysis failed to produce any significant differences between patients and controls. Therefore reversal learning seems to be relatively preserved in these patients. The task has not developed norms with which to compare patient performance. Therefore it is possible that control and patient performance were not significantly different, as control performance was equally impaired. The controls sample used was quite conservative (n=9) and therefore it is possible that controls failed to learn the concept of the task and hence produced no significant differences.

Inspection of individual performance according to single case analysis (see table 7), reveals that control performance was not as high as might have been expected. It is possible that controls failed to learn the basic concept of the task as both patterns were associated with wins and losses. Therefore controls switched between decks based on a strategy to select a rewarding pattern continuously. However, as each pattern contained both rewards and punishments to varying degrees, selecting patterns purely in search of rewards resulted in an excessive amount of switching. Pursuit of rewards instead of the pattern that was advantageous overall meant that the actual schedule of pattern reversal was not realised.

While poor control performance would appear to be a contributing factor as to why a significant difference was not found between groups, Hornak and colleagues (2004) found patients with large unilateral lesions were not impaired on the reversal learning task whereas patients with bilateral orbital/medial prefrontal lesions were significantly impaired. According to this evidence, it would seem that laterality may have an effect on performance. Hence, whilst each patient included in this study may have frontal involvement as discussed previously, it is possible that the damage may be unilateral only. As imaging data for the purposes of this study, it is not feasible to rule out this possibility completely. Successful performance on the reversal learning task for DLF patients in the study by Hornak and colleagues (2004) appeared to be related to whether the patients paid attention to the salient stimuli onscreen. Therefore DLF patients who did not attend to the salient stimuli had reduced performance compared to those who did attend to the salient stimuli. In this study, only 2 patients out of 7 who completed the task attended to the salient stimuli consistently. All others stated that the attended to the salient stimuli either inconsistently or not at all. DLF

involvement has previously been outlined in these patients due to impaired performance on the OIGT and SIGT. Therefore patients in this study may be defective on the reversal learning task due to DLF involvement, however as control performance was not significantly superior compared to patient's performance, no significant differences were found. This does not mean of course that OFC impairment can be ruled out.

4.4 Study Limitations

This study was not without its limitations. Test battery length was a considerable obstacle for data collection. The test battery lasted approximately 3 and a half hours for controls to complete in one session, and patients required approximately two 2 and a half hour sessions to complete the test battery. This was a substantial time period in which patients were required to pay attention and concentrate intently. Data was collected in collaboration with another project and whilst sharing data collection has significant advantages, again this did add to the length of the battery. If the battery were to consist only of the tasks required for the purposes of this study, it may have posed less of a problem for patients and resulted in more complete test batteries. As a result, 4 out of 12 patients did not complete the battery in full as they wished withdraw their participation and submit only the results of the tasks they had completed up to that point. In some cases, patients withdrew their participation as they became distressed by their performance on certain tasks, for example verbal fluency. Certain patients, who previously functioned at a high level as indicated by their WTAR score, found it distressing that they could no longer recall words spontaneously. Others withdrew their participation due to tiredness, frustration, or simply due to time constraints.

Researchers encouraged patients to take breaks whenever they pleased and again prompted patients to take a break or that the session end early, if the patient were becoming tired or agitated. However, many of the patients were very diligent and wanted to complete the test session as quickly as possible. This resulted in some patients becoming increasingly tired and/or distracted which cannot be ruled out as a contributing factor to impaired patient performance.

With regard to the IGT, several patients found 100 trails to be excessively long. Whilst the length of the task is necessary for reality and validity purposes, this was definitely a limitation of the task. Investigation into shortening the task would prove worthwhile in the future and possibly increase its

clinical usability. In relation to the reversal learning task, if participants selected the “bad deck” by chance at the start, this often meant that their balance remained negative throughout the game. This proved frustrating for patients and controls alike resulting in participants becoming apathetic rather than actively trying to solve the pattern in the task. A reversal learning task involving more than associations between abstract patterns and monetary rewards or punishments might engage participants to a greater extent. If participants were engaged in the task rather than frustrated, their scores might reflect their actual ability with greater reliability instead of measuring apathetic responses given purely to end the task rather than solve it. Of course this was not the case with every participant, however many did supply such feedback that it is necessary to report it as a limitation.

Administration of background tests was necessary to give a measure of patients premorbid and current functioning with which to compare results of experimental tasks. However if the experiment were to be repeated, careful consideration would be required as to which measures need to be included. Including too many background measures might increase battery length beyond patient’s abilities.

Lastly, the timeframe within which this study was conducted was a considerable limitation. Data collection was conducted over 6 weeks exactly, which considering the obstacles posed by travelling to patient’s homes to conduct testing, was a significantly limited timeframe. However given the use of nonparametric and single case analyses, the conservative sample was analysed appropriately.

4.6 Conclusions

In conclusion OIGT impaired performance was found in both FTD and MND patients compared to controls. This result was expected for FTD patients as the OFC is known to be implicated in FTD (The Lund & Manchester groups, 1994, Doherty et al., 2011), reversal learning (Rolls, 2000) and by extension the OIGT (Fellows & Farah, 2005). MND impaired performance may be explained by executive dysfunction which is a characteristic of MND patient’s cognitive profile (Neary, Snowden & Mann, 2000, Abrahams et al., 2000, 2005). SIGT performance was also impaired in FTD, MND and AD patients. The DLF could be implicated as both the OIGT and the SIGT were impaired (Fellows & Farah

et al., 2005). The frontal lobe can be affected in all three patient groups depending on their illness stage, with frontal involvement early on in FTD and affected much later in AD. There was no reversal learning deficit found in any patient group as control performance was much lower than expected. Therefore for future research, inclusion of patient's neuro-imaging results would give greater clarity as to which areas are affected at the time of testing. With the provision of neuro-imaging results clearer associations could be made between patient performance and the brain regions affected which in turn would shed greater light on decision-making impairment in these diseases.

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Appendices

Appendix A: Consent form

CONSENT FORM - Confidential

Title of project: **Brain regions associated with changes in social behaviour**

Name of Researcher: **Dr Sarah MacPherson**

Please initial box

1. I confirm that I have read and understand the information sheet dated 06.11.06 (version 2B) for the above study and have had the opportunity to ask questions. ☐

2. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my or my partner/relative/friend's medical care or legal rights being affected. ☐

3. I agree to take part in the above study. ☐

_____	_____	_____
Name of Carer	Date	Signature
_____	_____	_____
Name of Person taking consent (if different from researcher)	Date	Signature
_____	_____	_____
Researcher	Date	Signature

1 for carer; 1 for researcher

Appendix B: Test Order

	Name of Test	Important Notes
	First Visit	
☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐	Consent process and get signed consent Health screen? Especially controls IOWA Original – carer questionnaires- IRI X2, FrSBe carer IATS IATS explicit measures Faux Pas Reversal learning • demo • training • actual test Post-test questionnaire Verbal fluency – written generation + copy (timing) • "S" 5 minutes any letters • "C" 4 minutes 4 letter words only Spoken fluency P R W generation 1 minute each Eye-gaze Test part 1 ☐V1 AFF-COG/AFF-COG ☐V2 AFF-COG/ COG-AFF ☐V3 COG-AFF/ COG-AFF ☐V4 COG-AFF/ AFF-COG Eye-gaze Test part 2 physical motor Social Rule Break Cartoons	**Re-start computer** **Re-start computer**
	Second Visit	**Break (re-start computer)**
☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ 	IOWA Shuffled FEAST Spoken verbal fluency P R W control (typed out list + timing) Brixton Test WTAR WASI – Vocabulary WASI- Similarities Reading the Mind in the Eyes ACE-R VOSP- Cubes VOSP- Similarities Graded naming Test FrSBe-self IRI -self	 Start page 1 going to page 2 (DIFFICULT TO SCORE BE AWARE) (DO NOT DO VERBAL "P" only animals)

Appendix C: SDCRN Cover Letter

Psychology
SCHOOL *of* PHILOSOPHY, PSYCHOLOGY *and* LANGUAGE SCIENCES

The University of Edinburgh
7 George Square
Edinburgh EH8 9JZ

Telephone 0131 650 3440
or direct dial 0131 650
Fax 0131 650 3461
Email Psychology@ed.ac.uk

Edinburgh, 19th of May, 2011

Dear

Your details were given to me by the Scottish Dementia Clinical Research Network and I am writing to ask whether you would be willing to participate in a research project. The project is run by myself and colleagues at the University of Edinburgh and investigates aspects of language, thinking and behaviour in people with different neurological conditions.

Participation involves an interview including some problem solving tasks, and several questions about how you are feeling. In addition, someone who knows you very well like your partner, a relative or a friend, would be asked to answer some questions during a brief interview. The interview can be undertaken at your home, or if you prefer at the University of Edinburgh. I am enclosing copies of the information sheets, which provide more detailed information.

Please read the information sheets thoroughly prior to deciding whether you would like to take part in this study. It is entirely your choice whether or not to take part and you do not have to give any reason if you choose not to participate. Please also note that such a decision would not affect your treatment in any way.

If you are interested in helping with this work, I would be grateful if you could contact either Denise Rogers, Lindsay Oliver or myself, by phone or by e-mail, or by posting the attached reply slip (stamp included). Contact details are provided on the information sheets.

If you would like to obtain further information or talk to someone about the study before making your decision, please do not hesitate to contact me on 0131 650 3339. Thank you for your consideration.

Yours Sincerely,

Dr. Sharon Abrahams

Clinical Neuropsychologist

Appendix D: Cover letter for patients from Dr. Sharon Abraham's clinical files

Psychology
SCHOOL *of* PHILOSOPHY, PSYCHOLOGY *and* LANGUAGE SCIENCES

The University of Edinburgh
7 George Square
Edinburgh EH8 9JZ

Telephone 0131 650 3440
or direct dial 0131 650
Fax 0131 650 3461
Email Psychology@ed.ac.uk

Edinburgh, 1st of June, 2011

Dear

I am running a research study on aspects of language, thinking and behaviour in people with different neurological conditions and I wondered whether you would be willing to help in this research project.

Participation involves an interview including some problem solving tasks, very similar to those you undertook with me in our session together, and several questions about how you are feeling. In addition, someone who knows you very well like your partner, a relative or a friend, would be asked to answer some questions during a brief interview. The interview can be undertaken at your home, or if you prefer at the University of Edinburgh. I am enclosing copies of the information sheets, which provide more detailed information.

Please read the information sheets thoroughly prior to deciding whether you would like to take part in this study. It is entirely your choice whether or not to take part and you do not have to give any reason if you choose not to participate. Please also note that such a decision would not affect your treatment in any way.

If you are interested in helping with this work, I would be grateful if you could contact Denise Rogers, Lindsay Oliver or myself, either by phone, by e-mail or by posting the attached reply slip (stamp included). Contact details are provided on the information sheets.

If you would like to obtain further information or talk to someone about the study before making your decision, please do not hesitate to contact me on 0131 650 3339. Thank you for your consideration

Yours Sincerely,

Dr. Sharon Abrahams

Clinical Neuropsychologist

Appendix E: Patient information sheet

Psychology
SCHOOL *of* PHILOSOPHY, PSYCHOLOGY *and* LANGUAGE SCIENCES

The University of Edinburgh
7 George Square
Edinburgh EH8 9JZ

Telephone 0131 650 3440
or direct dial 0131 650
Fax 0131 650 3461
Email Psychology@ed.ac.uk

Information Sheet

Study title: "Language, Thinking and Behaviour in Different Neurological Conditions"

You are being invited to take part in a research study. Before you decide it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully and discuss it with others if you wish. Ask us if there is anything that is not clear or if you would like more information. Take time to decide whether or not you wish to take part.

What is the purpose of the study?

Clinical experience and research studies have shown that people with some neurological conditions have difficulties with language, thinking or behaviour. Using a battery of neuropsychological tests and questionnaires we aim to investigate what type of changes people with different neurological conditions experience in their language, thinking and behaviour. These results will be compared to a group of participants who do not have neurological problems.

Why have I been chosen?

We will be seeing a total of 20 people with various neurological conditions. We will also be seeing a total of 20 healthy control participants.

Do I have to take part?

It is up to you to decide whether or not to take part. If you do decide to take part you will be given this information sheet to keep and be asked to sign a consent form. If you decide to take part you are still free to withdraw at any time and without giving a reason. A decision to withdraw at any time, or a decision not to take part, will not affect the standard of care you receive, now or in the future.

What will happen to me if I take part?

The study will consist of an interview during which you will undertake a series of simple tasks, similar to word games and puzzles, some of which will take place on a computer. We will also ask you to complete a few questionnaires. The interview will be divided into two separate visits lasting approximately 2 hours each. The interviews can take place at your home at a time of your convenience, or at the Department of Psychology, University of Edinburgh, 7 George Square, if you prefer. You will be reimbursed for your travelling and parking expenses if you do decide to come to the University of Edinburgh.

During the interview we may sometimes ask to audio-record your voice whilst you are performing some of the tasks. We ensure that there will be nothing on the tape that could identify you in person and that these tapes will be destroyed once the data has been obtained.

As part of the study, we would separately like to ask a carer or relative who knows you well some questions. We are interviewing carers to try and get as many perspectives as possible on changes in behaviour that may, or may not occur in people with neurological problems. This will consist of them having a brief interview that will enquire about any changes that may have occurred since the onset of your neurological problems, and they will also be asked to complete some questionnaires.

This will take up to half an hour. Any responses given to us by your carer will remain confidential and we will not reveal them to you. You will also be asked to fill out a version of these questionnaires related to any changes you may have noticed yourself. We will not tell your carer how you responded to any of the questionnaires.

What do I have to do?

You will not have to come off medication or undergo any invasive procedure whatsoever. Most tests are in the forms of interviews, questionnaires or puzzle-like tests. If you are unable to write we will assist you in filling out the questionnaires. If you are unable to speak we may skip certain tests that rely on spoken answers.

If you agree to join the study, your General Practitioner will be sent a letter and informed that you have agreed to take part in this study. We will ask you for permission to inform your General Practitioner.

What are the possible disadvantages and risks of taking part?

We do not anticipate any health risks from taking part in this study. Due to the length of the interview you may find testing to be tiring, but you will be given plenty of opportunity to take breaks. If you feel distressed at all by the interview please do not hesitate to contact Dr Sharon Abrahams 0131 650 3339 (project leader).

What are the possible benefits of taking part?

There will be no direct benefit to you or your carer by taking part, and your individual results will not be revealed to you. However, we will make any future publications of the findings available to you. It is hoped that this research will improve our knowledge relating to various neurological conditions and may influence care practices in the future.

What if something goes wrong?

Whilst we do not anticipate any adverse effects from taking part in this study, if you are harmed by taking part in this research project, there are no special compensation arrangements. If you are harmed due to someone's negligence, then you may have grounds for a legal action but you may have to pay for it. Regardless of this, if you wish to complain, or have any concerns about any aspect of the way you have been approached or treated during the course of this study, the normal National Health Service complaints mechanisms should be available to you.

Will my taking part in this study be kept confidential?

All information which is collected about you during the research will be kept strictly confidential. Only people from the research team and the clinical team at your hospital may have access to your medical records and notes. Any information about you which leaves the hospital will have your name and address removed so that you cannot be recognised from it.

You will be allocated an anonymous ID code during testing which will be used in place of your name in our testing materials, computers or on any future publications.

What will happen to the results of the research study?

The results of the research will be published in appropriate peer-reviewed scientific journals for distribution to other healthcare professionals. Talks and presentations may be made at meetings and conferences. In all cases, your name and personal details will not be identified.

Who is organising the research?

The study is being organised by Dr. Sharon Abrahams and Dr. Sarah MacPherson from the University of Edinburgh, in collaboration with the Western General Hospital (Edinburgh).

Who has reviewed the study?

This study has been granted ethics approval by the Lothian Research Ethics Committee.

Contact for Further Information

If you wish to ask anything further, please contact us, the researchers, Denise Rogers or Lindsay Oliver:

Department of Psychology, PPLS

7 George Square

Edinburgh, EH8 9JZ

L.D.Oliver@sms.ed.ac.uk

D.C.Rogers@sms.ed.ac.uk

0131 651 5019

If your call is unanswered, please leave a message on the answering machine and we will get back to you as soon as possible.

Thank you for reading this information sheet. You will be given a copy to keep. If you have understood the contents of this sheet and wish to take part, please complete the consent sheet on the next page. If you have any questions please feel free to ask them now.

Appendix F: Carer information sheet

Psychology
SCHOOL *of* PHILOSOPHY, PSYCHOLOGY *and* LANGUAGE SCIENCES

The University of Edinburgh
7 George Square
Edinburgh EH8 9JZ

Telephone 0131 650 3440
or direct dial 0131 650
Fax 0131 650 3461
Email Psychology@ed.ac.uk

Information Sheet for Carers

Study title: "Language, Thinking and Behaviour in Different Neurological Conditions"

You are being invited to take part in a research study. Before you decide it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully and discuss it with others if you wish. Ask us if there is anything that is not clear or if you would like more information. Take time to decide whether or not you wish to take part.

What is the purpose of the study?

Clinical experience and research studies have shown that people with some neurological conditions have difficulties with language, thinking or behaviour. Using a battery of neuropsychological tests and questionnaires we aim to investigate what type of changes people with different neurological conditions experience in their language, thinking and behaviour. These results will be compared to a group of participants who do not have neurological problems.

Why have I been chosen?

Your partner, relative, or friend who has a neurological condition has volunteered to take part in this study and we would like to ask you some questions about how their behaviour may have changed since the onset of symptoms. We will be seeing a total of 20 people with various neurological conditions. We will also be seeing a total of 20 healthy control participants.

Do I have to take part?

It is up to you to decide whether or not to take part. If you do decide to take part you will be given this information sheet to keep and be asked to sign a consent form. If you decide to take part you are still free to withdraw at any time and without giving a reason. A decision to withdraw at any time, or a decision not to take part, will not affect the standard of care which you or the person with neurological problems receives, now or in the future.

What will happen to me if I take part?

The study will consist of one interview during which you will be asked some questions relating to any changes you may have noticed in the behaviour of your partner/relative/friend with neurological problems. This should take approximately 30 minutes. Any responses given to us by you will remain confidential.

What do I have to do?

You will not have to take medication or undergo any invasive procedure whatsoever. Tests are in the forms of an interview and questionnaires.

What are the possible disadvantages and risks of taking part?

We do not anticipate any health risks from taking part in this study. If you feel distressed at any time during the interview it is important that you let the interviewer know straight away. If you feel distressed after the interview, please contact Dr. Sharon Abrahams 0131 650 3339 (project leader).

What are the possible benefits of taking part?

There will be no direct benefit to you or your partner/relative/friend by taking part, and your individual results will not be revealed to you. However, we will make any future publications of the findings available to you. It is hoped that this research will

improve our knowledge relating to various neurological conditions and may influence care practices in the future.

What if something goes wrong?

Whilst we do not anticipate any adverse effects from taking part in this study, if you are harmed by taking part in this research project, there are no special compensation arrangements. If you are harmed due to someone's negligence, then you may have grounds for a legal action but you may have to pay for it. Regardless of this, if you wish to complain, or have any concerns about any aspect of the way you have been approached or treated during the course of this study, the normal National Health Service complaints mechanisms should be available to you.

Will my taking part in this study be kept confidential?

All information which is collected about you during the research will be kept strictly confidential, and we will not tell your partner/relative/friend about your answers. Only people from the research team will see your information. You will be allocated an anonymous ID code during testing which will be used in place of your name in our testing materials or on any future publications.

What will happen to the results of the research study?

The results of the research will be published in appropriate peer-reviewed scientific journals for distribution to other healthcare professionals. Talks and presentations may be made at meetings and conferences. In all cases, your name and personal details will not be identified.

Who is organising the research?

The study is being organised by Dr. Sharon Abrahams, Dr. Sarah MacPherson, Denise Rogers and Lindsay Oliver from the University of Edinburgh, in collaboration with the Western General Hospital (Edinburgh).

Who has reviewed the study?

This study has been granted ethics approval by the Lothian Research Ethics Committee.

Contact for Further Information

If you wish to ask anything further, please contact us, the researchers, Denise Rogers or Lindsay Oliver:

Department of Psychology, PPLS

7 George Square

Edinburgh, EH8 9JZ

L.D.Oliver@sms.ed.ac.uk

D.C.Rogers@dmd.ed.ac.uk

0131 651 5019

If your call is unanswered, please leave a message on the answering machine and we will get back to you as soon as possible.

Thank you for reading this information sheet. You will be given a copy to keep. If you have understood the contents of this sheet and wish to take part, please complete the consent sheet on the next page. If you have any questions please feel free to ask them now.

Appendix G: GP letter

Psychology
SCHOOL *of* PHILOSOPHY, PSYCHOLOGY *and* LANGUAGE SCIENCES

The University of Edinburgh
7 George Square
Edinburgh EH8 9JZ

Telephone 0131 650 3440
or direct dial 0131 650
Fax 0131 650 3461
Email Psychology@ed.ac.uk

Dr *<Name of GP>*

<Name of Health Centre>

<Street>

<City>

<Postal Code>

DD Month YYYY

Dear Dr *<Name of GP>*

RE: *<Title + Patient first- and surname>* (DOB *dd/mm/yy*)

<Street>

<City>

<Postal Code>

I am writing to inform you that *<Title + Patient surname>* has agreed to participate in a

research study entitled <*Enter study title depending on patient group*> with Edinburgh University. This is a non-invasive study involving interviews in which participants undertake a number of neuropsychological tests (language and problem solving) and questionnaires addressing issues of behaviour and emotion changes. We are contacting you to inform you of <*Title* + *Patient surname's*> participation in accordance with ethical guidelines. I enclose an information sheet.

Please do not hesitate to contact me if there are any further queries.

Yours sincerely

Dr. Sharon Abrahams

Senior Lecturer in Human Cognitive Neuroscience &

Clinical Neuropsychologist

- Enclosed: Participant Information Sheet

Appendix H: Response Slip

001

Response Slip

[ ] I would like to be contacted further about this study.

[ ] I would not like to be contacted further about this study.

Name:_____ Phone Number: _____

Appendix I: WAIS Exclusion Criteria

EXCLUSION CRITERIA

PLEASE LET THE EXPERIMENTER KNOW IF ANY OF THE FOLLOWING APPLY. YOU DO NOT HAVE TO STATE WHICH ONE.

- **Colour-blindness**
- **Uncorrected hearing loss**
- **Uncorrected visual impairment**
- **Current treatment for alcohol or drug dependence**
- **Seeing a doctor or other professional for memory problems or problems with thinking**
- **A condition that would prevent arm movement and/or the use of both hands**
- **Any period of unconsciousness for 5 minutes or more**
- **Head injury resulting in hospitalisation for more than 24 hours**
- **Currently taking antidepressant, anti-anxiety, or anti-psychotic medication**
- **Medical or psychiatric condition that could potentially affect cognitive functioning, such as:**
    - **Stroke**
    - **ECT (electric shock treatment)**
    - **Epilepsy**
    - **Brain surgery**
    - **Encephalitis**
    - **Meningitis**
    - **Multiple sclerosis**
    - **Parkinson's disease**

- **Huntington's chorea**
- **Alzheimer's dementia**
- **Schizophrenia**
- **Bipolar disorder**